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Author manuscript

Org Lett. Author manuscript; available in PMC 2023 April 22.

Published in final edited form as:

Org Lett. 2020 November 06; 22(21): 8665–8669. doi:10.1021/acs.orglett.0c03257.

The Tethered Silanoxymercuration of Allylic Alcohols

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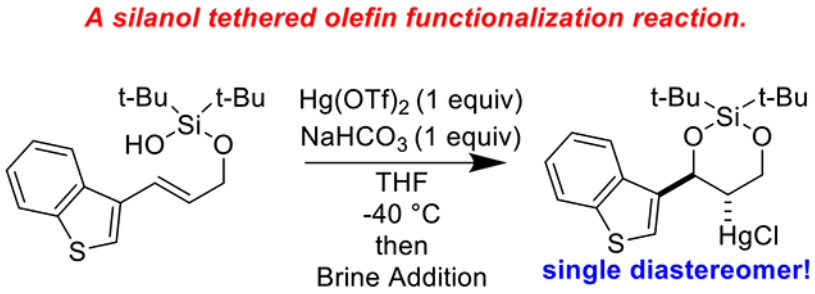
Abstract

We present the first examples of tethered olefin functionalization reactions using a silanol auxiliary. A range of allylic alcohols are readily condensed with di-*tert*-butylsilyl bis(trifluoromethanesulfonate) to form allylic silanols. When treated with $Hg(OTf)_2$ and $NaHCO_3$, these silanols facilely transform into cyclic silanediol organomercurial compounds. In most cases, the reactions are exquisitely diastereoselective. The scale can be increased more than ten-fold without loss of yield and selectivity. We demonstrate that the product silanediols are versatile synthons for a variety of further reactions.

Graphical Abstract



The family of organomercurials has earned an unfortunate reputation, largely due to the actions of a minority of its members.[1, 2] Nevertheless, the majority of higher order organomercurial compounds are crystalline, air-stable, and, when treated with appropriate respect, no more dangerous than most chemicals encountered in the organic laboratory.[3] The C–Hg linkage is essentially covalent, making it a most unique and versatile organometallic bond. [4–6] Our laboratory is deeply invested in the field of tethered olefin functionalization reactions.[7–9] In such reactions, a nucleophilic auxiliary (the "tether") is appended to an alcohol or amine and then cyclized onto a pendant alkene. Here, we disclose our most recent contribution to this area, a cyclization reaction of allylic silanols into cyclic silanediol mercury chloride compounds. Allylic alcohols can be readily transformed into allylic silanols using a combination of di-*tert*-butylsilyl bis(trifluoromethanesulfonate)[10] and

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Supporting Information. Experimental and characterization data as well crystallographic data for Compound 31 is included in the supplementary information. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

imidazole; the free OH of the silanol tether serves as a convenient nucleophile for olefin attack.

The resulting cyclic silanediol compounds, reminiscent of intermediates *en route* to polyol natural products (Figure 1),[11–17] are synthons for a variety of further transformations.

Silanol auxiliaries have been popularized by Gevorgyan and co-workers as directing groups in C–H functionalization reactions.[18, 19] There is one example from the Lee laboratory of the use of silanols for gold catalyzed alkyne functionalization[20], and an example of a silylperoxidation reaction of homoallylic alcohols from the Woerpel laboratory.[21] Nevertheless, our survey of the literature revealed *no examples* of the silanol tether employed in alkene functionalization. Our work has been directly inspired by the pioneering contributions of Overman[22, 23] and Leighton[24–28], who demonstrated that acetal tethers could be used for the mercuric-salt mediated functionalization of olefins (Scheme 1).[29, 30]

Optimization of our silanol-tethered alkene functionalization reaction (Table 1) was performed with (E)-(but-2-en-1-yloxy)di-tert-butylsilanol which was synthesized in one step from crotyl alcohol and di-*tert*-butylsilyl bis(trifluoromethanesulfonate) (See Supporting Information for full experimental procedures). With 1 equivalent of $Hg(OCOCF_3)_2$, we were pleased to observe formation of 22% of desired cyclic silanediol (Table 1, **Entry 1**), giving us hope that our conceived reaction was viable. There was little improvement with increase of temperature (Table 1, **Entry 2**), equivalents of $Hg(OCOCF_3)_2$ (Table 1, **Entry 3**), or time (Table 1, **Entry 4**). We hypothesized that adventitious trifluoroacetic acid, formed as a byproduct of cyclization, was deleterious to reaction progress. Accordingly, we tested K_2CO_3 and $NaHCO_3$ in varying equivalents (Table 1, **Entries 5-7**) as base additives. Nevertheless, we observed little change in reaction performance. Reducing the temperature to −40 °C was markedly deleterious (Table 1, **Entry 8**). To our amazement and excitement, at this temperature, simply switching to Nishizawa's salt ($Hg(OTf)_2$),[31] in combination with $NaHCO_3$ (1 equivalent) afforded clean and high-yielding conversion to the desired product (Table 1, **Entry 9**). It should be noted that the use of 1 equivalent of $NaHCO_3$ was *critical* for reaction performance! In its absence, a complex mixture of decomposition products was observed (Table 1, **Entry 10**).

Our optimized protocol utilizing $Hg(OTf)_2$ (1 equivalent) and $NaHCO_3$ (1 equivalent) at −40 °C in THF was compatible with a wide array of alkenyl silanol substrates (Scheme 2). The silanol auxiliary could be appended to both primary allylic alcohols as well as secondary ones (Scheme 2, **Entry 9**). In all but two instances (Scheme 2, **Entry 10**), the cyclization reaction proceeded with excellent diastereoselectivity (>20:1), with the pendant alkyl or aryl group and mercury chloride substituent in a *trans* relationship. A crystal structure of **31** (Scheme 2, **Entry 6**) unambiguously established this stereochemistry. It is remarkable to note that even with products containing 3 stereocenters (Scheme 2, **Entry 9**), only a single diastereomer was observed. We hypothesize that a chair-like transition state during silanoxy-mercuration is responsible for this excellent diastereoselectivity (Scheme 3). The reaction was tolerant of a wide variety of alkyl and aryl substituents attached to the olefin. Ethers (Scheme 2, **Entries 2, 5, 6, 7**), halogens (Scheme 2, **Entry 6**), and several heterocycles (Scheme 2, **Entries 7 and 8**) were all compatible. Di-substituted *trans*-olefins

were the most competent substrates in this cyclization. While di-substituted *cis*-olefins also reacted (Scheme 2, **Entry 11**), the yield of cyclized product dropped. Furthermore, an *endo* mode of cyclization was strongly preferred; *exo* cyclization (Scheme 2, **Entry 12**) proceeded in only low yield.

With tri-substituted alkenes, the cyclization reaction proceeded only partially, if at all (Scheme 4). Nevertheless, in these reactions, alcohol products were isolated, which themselves may be valuable intermediates for further derivatization.[3]

We were pleased to find that our cyclization reaction scaled greater than 10-fold with no loss in yield or selectivity (Scheme 5).

Furthermore, as we had envisioned at the conception of this project, the cyclic silanediol organo-mercury products could be used as starting materials for a variety of further transformations, including hydroxylation,[32–34] demercuration, [35–38] and iodination[39–41] (Scheme 6A–C).

In summary, we present the first tethered olefin functionalization using a silanol auxiliary. The silanol tether could be conveniently appended to a variety of primary and secondary alcohols *via* condensation with di-*tert*-butylsilyl bis(trifluoromethanesulfonate). $Hg(OTf)_2$ mediated cyclization proceeded with high diastereoselectivity and afforded cyclic silanediol mercury chloride products. The reaction was scalable greater than ten-fold and the products were readily amenable for further demercurative transformations. We expect this reaction to find much application in the pursuit of important polyhydroxylated compounds.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

This work was supported by start-up funding provided jointly by the University of Kansas Office of the Provost and the Department of Medicinal Chemistry as well as an NIH COBRE Chemical Biology of Infectious Diseases Pilot Project Grant to Shyam Sathyamoorthi (P20GM113117). We thank Dr. Victor Day (University of Kansas) for X-ray crystallography analysis. Support for the NMR instrumentation was provided by the NIH Shared Instrumentation Grant No. S10RR014767. We thank Professor Frank Schoenen, Professor Apurba Dutta, Professor Ryan Altman, and Mr. Cornelius Ndi for timely donation of a Lauda Brinkmann IC-6 immersion cooler chiller.

REFERENCES

1. Yokoyama H, Lecture on Methylmercury Poisoning in Minamata (MPM). In Mercury Pollution in Minamata, Yokoyama H, Ed. Springer Singapore: Singapore, 2018; pp 5–51.
2. Hong Y-S; Kim Y-M; Lee K-E, Methylmercury Exposure and Health Effects. J Prev Med Public Health 2012, 45, 353–363. [PubMed: 23230465]
3. Larock RC, Organomercury Compounds in Organic Synthesis. Angew. Chem. Int. Ed 1978, 17, 27–37.
4. Larock RC, Hydrogen and Halogen Substitution. In Organomercury Compounds in Organic Synthesis, Larock RC, Ed. Springer Berlin Heidelberg: Berlin, Heidelberg, 1985; pp 155–186.
5. Larock RC, Synthesis of Heteroatom-Containing Compounds. In Organomercury Compounds in Organic Synthesis, Larock RC, Ed. Springer Berlin Heidelberg: Berlin, Heidelberg, 1985; pp 187–239.

6. Larock RC, Alkene and Alkyne Addition and Substitution Reactions. In Organomercury Compounds in Organic Synthesis, Larock RC, Ed. Springer Berlin Heidelberg: Berlin, Heidelberg, 1985; pp 263–308.
7. Shinde AH; Sathyamoorthi S, Oxidative Cyclization of Sulfamates onto Pendant Alkenes. Org. Lett 2020, 22, 896–901. [PubMed: 31927967]
8. Shinde AH; Nagamalla S; Sathyamoorthi S, N-arylated oxathiazinane heterocycles are convenient synthons for 1,3-amino ethers and 1,3-amino thioethers. Med. Chem. Res 2020, 29, 1223–1229.
9. Thomas AA; Nagamalla S; Sathyamoorthi S, Salient features of the aza-Wacker cyclization reaction. Chem. Sci 2020, 11, 8073–8088. [PubMed: 34123081]
10. Corey EJ; Hopkins PB, Diisopropylsilyl ditriflate and di-tert-butysilyl ditriflate: new reagents for the protection of diols. Tetrahedron Lett. 1982, 23, 4871–4874.
11. Trost BM; Caldwell CG, The di-t-butylsilylene protecting group for diols. Tetrahedron Lett. 1981, 22, 4999–5002.
12. Arefolov A; Panek JS, Crotylsilane Reagents in the Synthesis of Complex Polyketide Natural Products: Total Synthesis of (+)-Discodermolide. J. Am. Chem. Soc 2005, 127, 5596–5603. [PubMed: 15826198]
13. Obringer M; Barbarotto M; Choppin S; Colobert F, Efficient and Stereoselective Access to the Polyol Fragment C9–C16 of Ansamycin Antibiotics. Org. Lett 2009, 11, 3542–3545. [PubMed: 19624101]
14. Chan C; Zheng S; Zhou B; Guo J; Heid RM; Wright BJD; Danishefsky SJ, The Solution to a Deep Stereochemical Conundrum: Studies toward the Tetrahydroisoquinoline Alkaloids. Angew. Chem. Int. Ed 2006, 45, 1749–1754.
15. Paterson I; Mühlthau FA; Cordier CJ; Housden MP; Burton PM; Loiseleur O, Toward the Total Synthesis of the Brasilinolides: Stereocontrolled Assembly of a C1–C19 Polyol Segment. Org. Lett 2009, 11, 353–356. [PubMed: 19072327]
16. Chen C-L; Namba K; Kishi Y, Attempts To Improve the Overall Stereoselectivity of the Ireland–Claisen Rearrangement. Org. Lett 2009, 11, 409–412. [PubMed: 19128191]
17. Caspi DD; Garg NK; Stoltz BM, Heterogeneous Reductive Isomerization Reaction Using Catalytic Pd/C and H2. Org. Lett 2005, 7, 2513–2516. [PubMed: 15932236]
18. Parasram M; Gevorgyan V, Silicon-Tethered Strategies for C–H Functionalization Reactions. Acc. Chem. Res 2017, 50, 2038–2053. [PubMed: 28771325]
19. Wang Y; Gevorgyan V, General Method for the Synthesis of Salicylic Acids from Phenols through Palladium-Catalyzed Silanol-Directed C-H Carboxylation. Angew. Chem. Int. Ed 2015, 54, 2255–2259.
20. Lee E; Ryu T; Park Y; Park S; Lee PH, Tandem Gold-Catalyzed Hydrosilyloxylation–Aldol and –Mannich Reaction with Alkynylaryloxysilanols in 6-exo Mode. Adv. Synth. Catal 2013, 355, 1585–1596.
21. Oswald JP; Woerpel KA, Cobalt-Catalyzed Intramolecular Silylperoxidation of Unsaturated Diisopropylsilyl Ethers. J. Org. Chem 2019, 84, 7564–7574. [PubMed: 31046281]
22. Overman LE; Campbell CB, Hemiacetal mediated reactions. Directed synthesis of diols and acetals. J. Org. Chem 1974, 39, 1474–1481.
23. Overman LE, Intramolecular delivery of a water equivalent in the oxymercuration reaction. Conversion of an allylic alcohol into a cis- vicinal diol. J. Chem. Soc., Chem. Commun 1972, 1196–1198.
24. Dreher SD; Leighton JL, Formal Total Synthesis of Mycoticin A. J. Am. Chem. Soc 2001, 123, 341–342. [PubMed: 11456525]
25. Sarraf ST; Leighton JL, Oxymercuration of Homoallylic Alcohol Derived Hemiacetals: Diastereoselective Synthesis of Protected 1,3-Diols. Org. Lett 2000, 2, 403–405. [PubMed: 10814334]
26. Hornberger KR; Hamblett CL; Leighton JL, Total Synthesis of Leucascandrolide A. J. Am. Chem. Soc 2000, 122, 12894–12895.
27. Sarraf ST; Leighton JL, Rhodium-Catalyzed Formylation of Organomercurials: Application to Efficient Polyol Synthesis. Org. Lett 2000, 2, 3205–3208. [PubMed: 11009382]

28. Dreher SD; Hornberger KR; Sarraf ST; Leighton JL, Yb(OTf)3-Catalyzed Oxymercuration of Homoallylic Alcohol-Derived Hemiacetals and Hemiketals. Org. Lett 2000, 2, 3197–3199. [PubMed: 11009380]
29. Evans PA; Grisin A; Lawler MJ, Diastereoselective Construction of syn-1,3-Dioxanes via a Bismuth-Mediated Two-Component Hemiacetal/Oxa-Conjugate Addition Reaction. J. Am. Chem. Soc 2012, 134, 2856–2859. [PubMed: 22296255]
30. Bonini C; Campaniello M; Chiummiento L; Videtta V, Stereoselective synthesis of versatile 2-chloromercurium-3,5-syn-dihydroxy esters via intramolecular oxymercuration. Tetrahedron 2008, 64, 8766–8772.
31. Nishizawa M; Imagawa H; Yamamoto H, A new catalyst for organic synthesis: mercuric triflate. Org. Biomol. Chem 2010, 8, 511–521. [PubMed: 20090963]
32. Raeppel F; Weibel J-M; Heissler D, Synthesis of the trans-syn-trans perhydrobenz[e]indene moiety of the stellettins and of the stelliferins. Tetrahedron Lett. 1999, 40, 6377–6381.
33. Khalaf JK; Datta A, An Efficient and Highly Stereocontrolled Route to Bulgecinine Hydrochloride. J. Org. Chem 2004, 69, 387–390. [PubMed: 14725451]
34. Crich D; Natarajan S; Crich JZ, Synthesis of the taxol AB-system by olefination of an A-ring C1 ketone and direct B-ring closure. Tetrahedron 1997, 53, 7139–7158.
35. Andrey O; Glanzmann C; Landais Y; Parra-Rapado L, 1,3-Asymmetric induction in electrophilic addition onto homoallylsilanes. An approach towards the total synthesis of (+/−)-kumausyne. Tetrahedron 1997, 53, 2835–2854.
36. Liu T-Z; Li J-M; Isobe M, Synthetic Studies on Ciguatoxin—Synthesis of H–I–J Ring System. Tetrahedron 2000, 56, 10209–10219.
37. Oikawa H; Toyomasu T; Toshima H; Ohashi S; Kawaide H; Kamiya Y; Ohtsuka M; Shinoda S; Mitsuhashi W; Sassa T, Cloning and Functional Expression of cDNA Encoding Aphidicolan-16β-ol Synthase: A Key Enzyme Responsible for Formation of an Unusual Diterpene Skeleton in Biosynthesis of Aphidicolin. J. Am. Chem. Soc 2001, 123, 5154–5155. [PubMed: 11457369]
38. McDonald FE; Ishida K; Hurtak JA, Stereoselectivity of electrophile-promoted oxacyclizations of 1,4-dihydroxy-5-alkenes to 3-hydroxytetrahydropyrans. Tetrahedron 2013, 69, 7746–7758.
39. Stevens RV; Albizati KF, Synthetic approach to the amphilectane diterpenes: the use of nitriles as terminators of carbocation-olefin cyclizations. J. Org. Chem 1985, 50, 632–640.
40. Bloodworth AJ; Bowyer KJ; Mitchell JC, Stereochemical evidence for an alkylated perepoxide intermediate. J. Org. Chem 1987, 52, 1124–1128.
41. Eaton PE; Daniels RG; Casucci D; Cunkle GT; Engel P, Amide activation for cyclopropane ortho-lithiation. J. Org. Chem 1987, 52, 2100–2102.

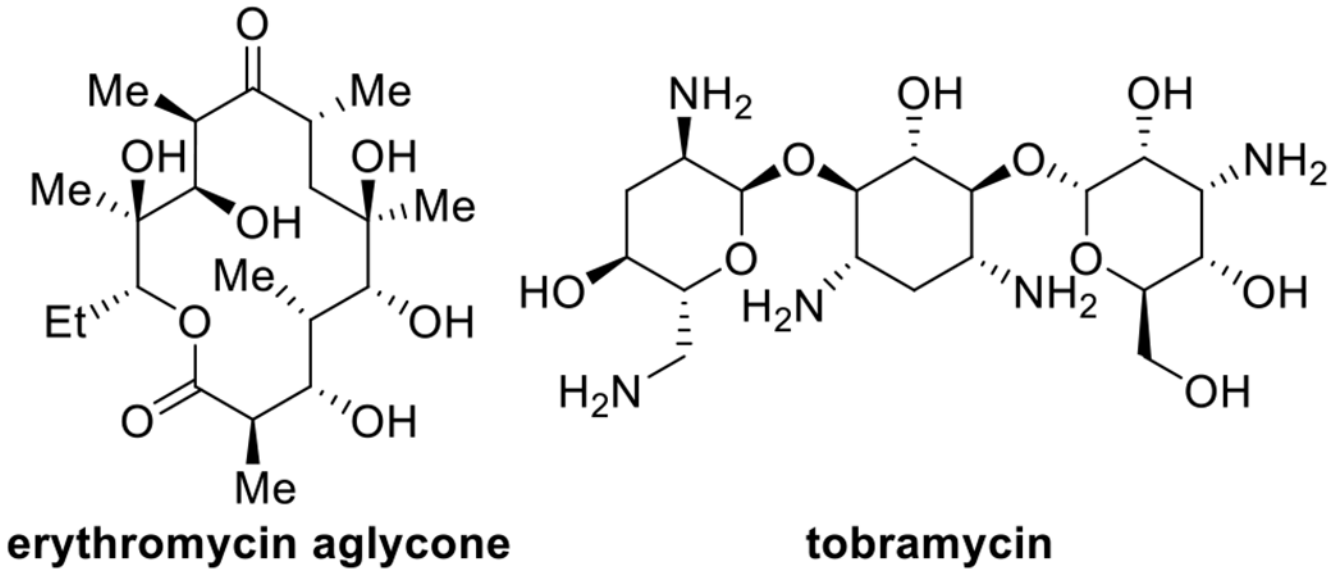
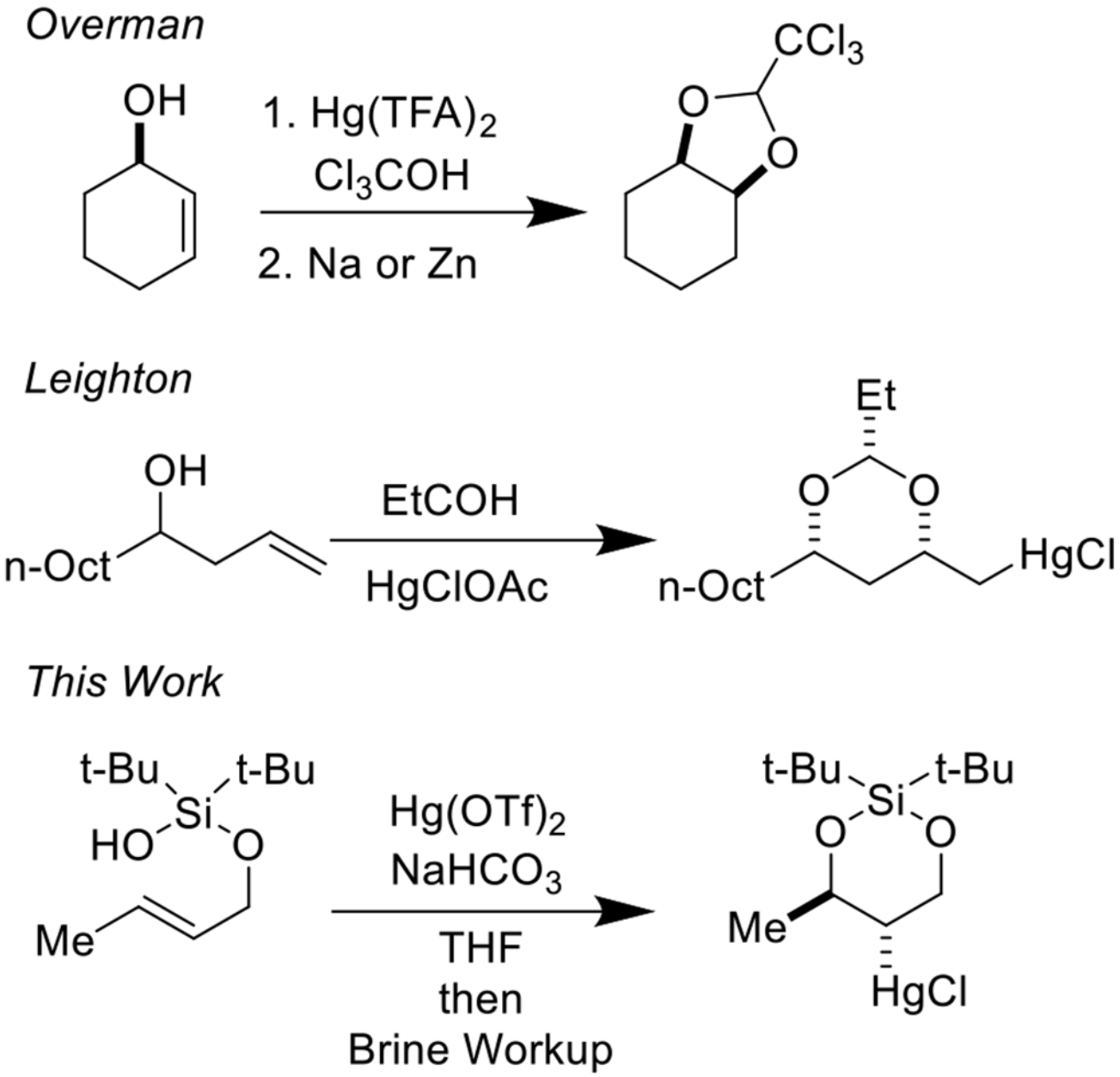
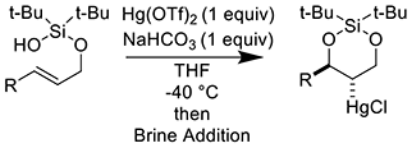
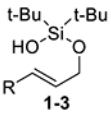
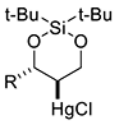
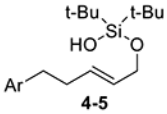
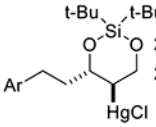
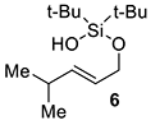
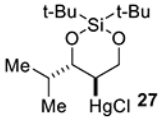
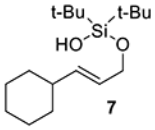
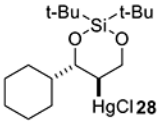
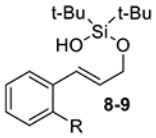
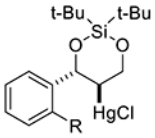
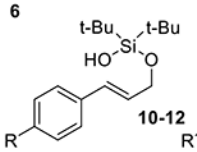
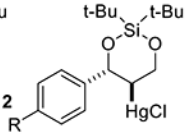
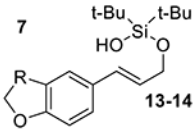
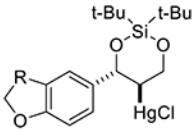
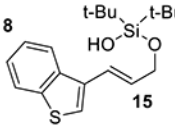
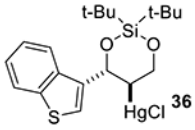


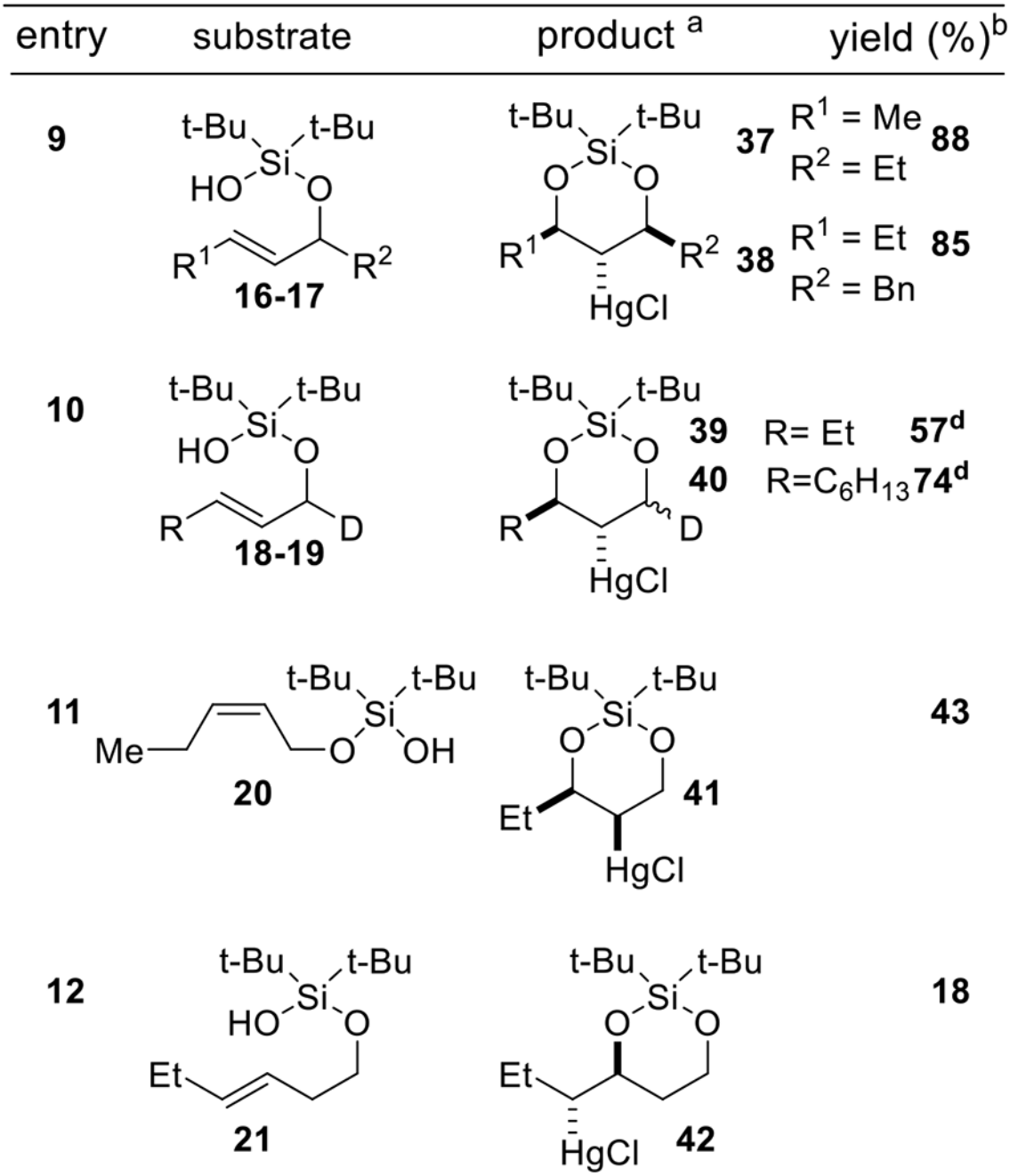
Figure 1.
Many antibiotics are polyhydroxylated compounds.



Scheme 1.
A strategy for the conversion of alkenyl alcohols into diol synthons.



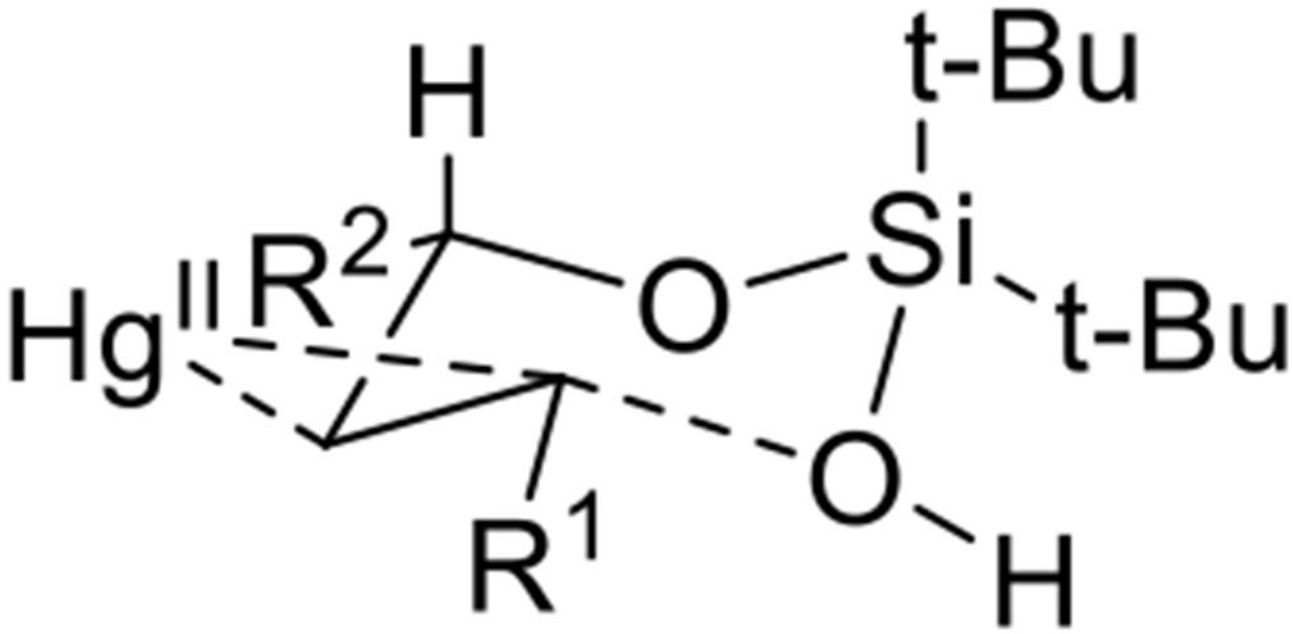
entry	substrate	product [a]	yield (%)[b]
1	 1-3		**22** R = Me **70** **23** R= n-Pr **63** **24** R= C_9H_{19} **70**
2	 4-5		**25** Ar = Ph **68** **26** Ar=pOMeC_6H_4 **61**
3	 6	 **27**	**54**
4	 7	 **28**	**62**
5	 8-9		**29** R = H **60** **30** R = OMe **52**
6	 10-12		**31** R = F **59**[c] **32** R = OMe **43** **33** R =  **56**
7	 13-14		**34** R = O **55** **35** R = CH_2 **51**
8	 15	 **36**	**52**



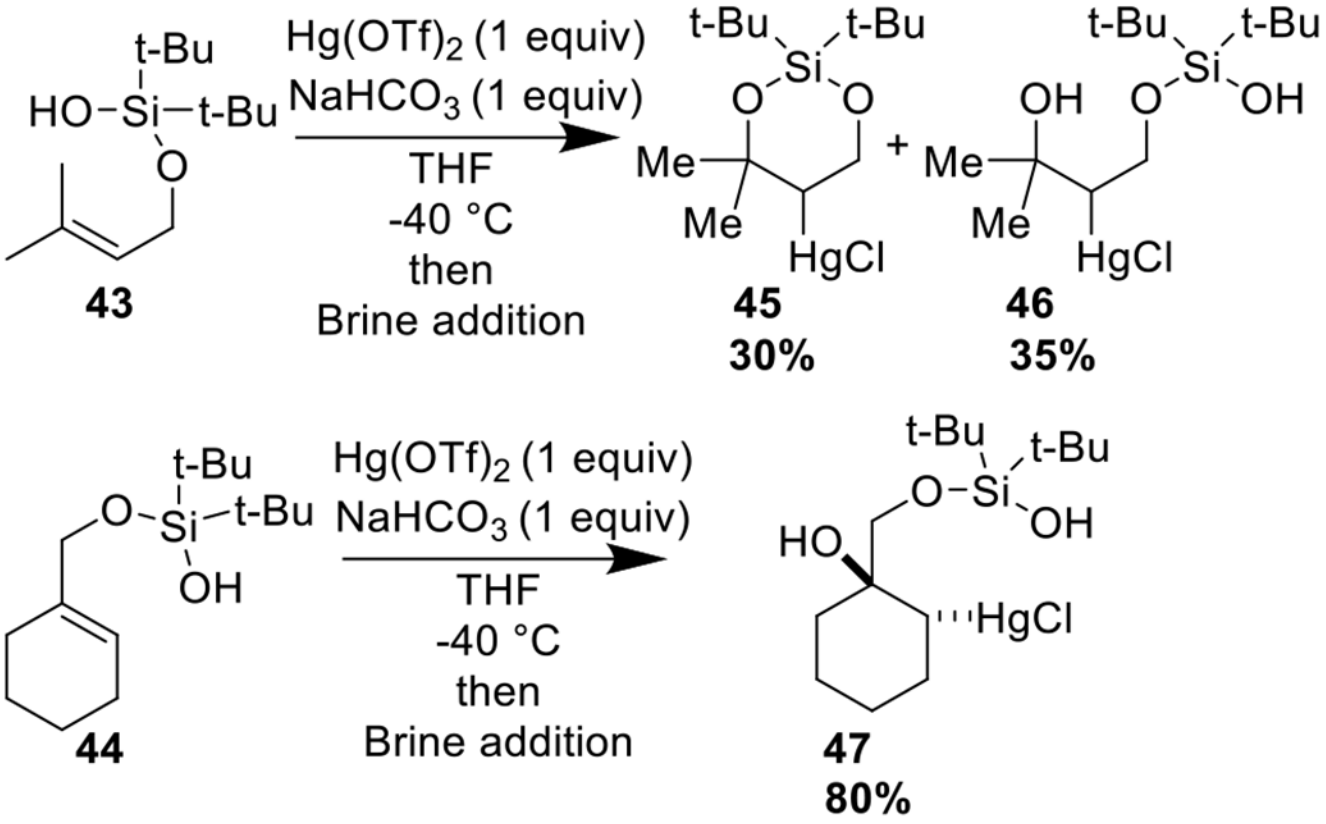
Scheme 2.

Substrate Scope

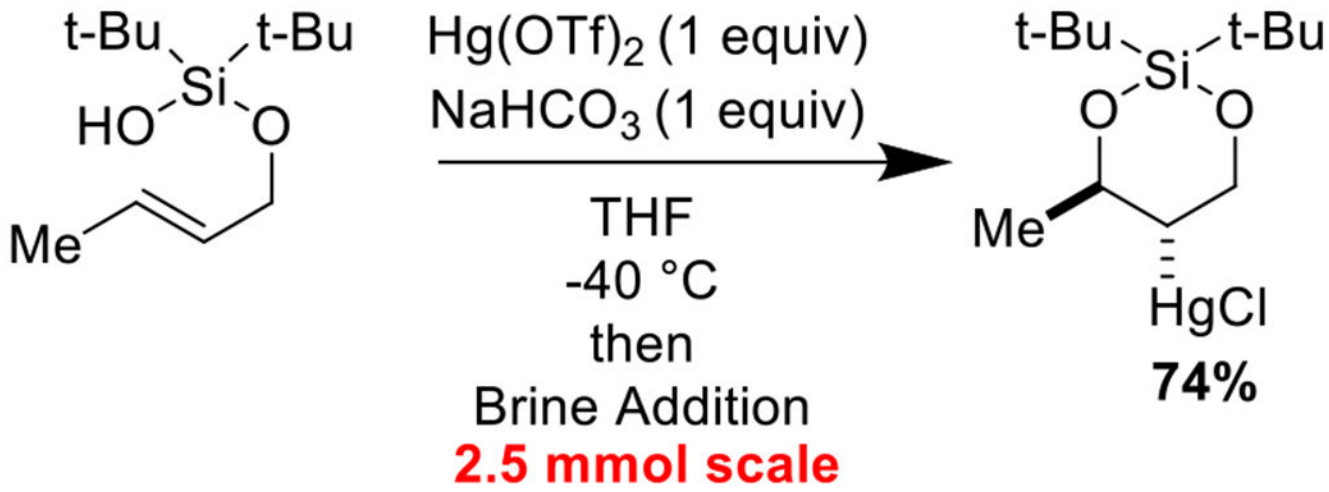
[a]reactions conducted on a 0.2 mmol scale and relative stereochemistry is shown in all cases. [b]Isolated yields. [c]Crystallographic information deposited in the Cambridge Database (CCDC), Number 2032765 [d]*dr* = 1:1.



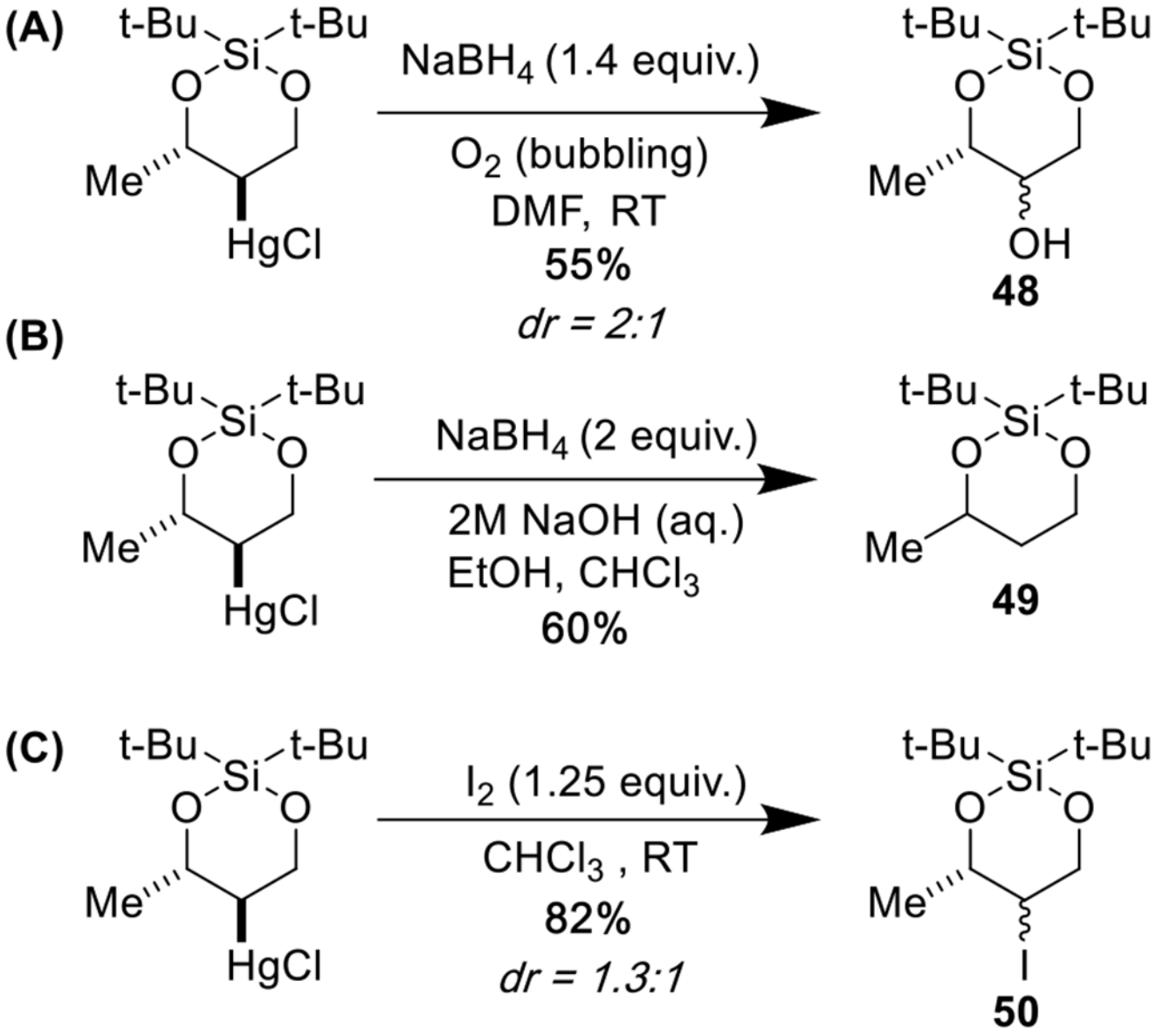
Scheme 3.
A chair-like transition state likely underlies the high diastereoselectivity of cyclization.



Scheme 4.
Some substrates do not fully cyclize but still form valuable diol products.



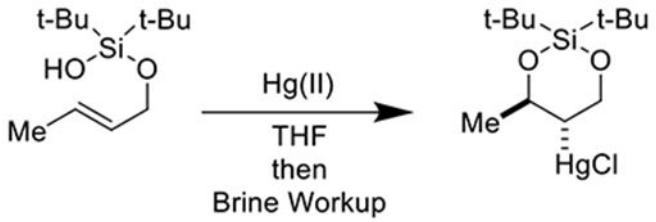
Scheme 5.
Cyclization scales greater than 10-fold with no loss of yield and selectivity.



Scheme 6.
The C–Hg organometallic bond is highly versatile.

Table 1.

Reaction Optimization



Entry[a]	Hg (II)(equiv.)	Base	Temp/Time	P/RSM
1	$Hg(OCOCF_3)_2$(1)	None	23 °C, 1h	22/45
2	$Hg(OCOCF_3)_2$(1)	None	40 °C, 1h	25/28
3	$Hg(OCOCF_3)_2$ (2)	None	23 °C, 1h	29/30
4	$Hg(OCOCF_3)_2$ (1)	None	23 °C, 16h	31/13
5	$Hg(OCOCF_3)_2$ (1)	K_2CO_3 (1)	23 °C, 16h	34/18
6	$Hg(OCOCF_3)_2$ (1)	$NaHCO_3$ (1)	23 °C, 16h	34/18
7	$Hg(OCOCF_3)_2$ (1)	$NaHCO_3$ (2)	23 °C, 16h	38/8
8	$Hg(OCOCF_3)_2$ (1)	$NaHCO_3$ (1)	−40 °C, 16h	6/63
9	$Hg(OTf)_2$ (1)	$NaHCO_3$ (1)	−40 °C, 16h	67/<5
10	$Hg(OTf)_2$ (1)	None	−40 °C, 16h	__[b]

[a]Yield estimated with methyl phenyl sulfone as a ^{1}H NMR internal standard.

[b]Complex mixture of products.